REMARKS

Upon entry of the foregoing amendment, claims 1-27 are pending in this application, with claims 1, 5, 10, 15 and 23 being the independent claims. Support for the amendments to claims 1, 5, 10, 15, 21 and 23 is found, *inter alia*, in original claims 1, 5, 10, 15, 21 and 23; on page 1, lines 13-15; page 5, lines 12-20; and, elsewhere throughout the specification. Support for the amendment to claim 3 is found in original claim 3. The amendment is made to correct antecedent basis. Support for the amendments to claims 21 and 26 ("modified") is found, *inter alia*, in original claims 21 and 26. The amendments are made to correct antecedent basis. Other amendments to claims 5 ("generating") and 10 ("generating" and "generated") are made to correct grammatical errors and support for the amendments to those claims is found in original claims 5 and 10. Support for the amendment to claim 10 ("disrupted") is found, *inter alia*, on page 8, line 7, and elsewhere throughout the specification. It is believed no new matter has been introduced by these amendments and entry thereof is respectfully submitted.

The Office Action dated January 30, 2002 (Paper No. Not Assigned) has been carefully reviewed. In view of the amendments above and the following remarks, reconsideration and withdrawal of the outstanding rejections and the timely allowance of the pending claims is respectfully requested.

Priority

The Examiner's acknowledgement of priority to provisional application 60/109,797 filed 8/4/98 is noted.

Oath/Declaration

The petition under 37 CFR § 1.47(a) filed October 9, 2001 has been dismissed. Applicants will submit a subsequent petition under 37 CFR § 1.47(a) requesting that one of the two joint inventors be allowed to file the application on behalf of himself and the other non-signing joint-inventor.

Claim Objections

At page 2 of the Office Action, the Office objects to claims 1, 5, 10, 15 and 23 because of certain informalities. The Office asserts the word "glycoprotein" should precede the abbreviation "GP" in any independent claim; that the phrase "An cell" in claim 23 is grammatically improper; and that step (c) in claim 10 is improperly referring to itself.

In reply, the claims have been amended as suggested by the Office. Claims 1, 5, 10, 15, 21 and 23 have been amended to include the word "glycoprotein" before the first appearance of "GP" in claims 1, 5, 10, 15 and 23. Claims 10 and 23 have been amended to correct the grammatical errors noted by the Office. The amendments are believed to overcome the objections, and withdrawal of the objections is respectfully requested.

REJECTION UNDER 35 U.S.C. § 101

At page 2 of the Office Action, the Office rejects claims 1-27 under 35 U.S.C. § 101 because the claimed invention lacks patentability due to its not being supported by either specific and/or substantial utility or a well-established utility. The rejection is respectfully traversed.

At pages 5-6 of the Office Action, the Office asserts the claimed invention does not have a credible utility, lacks a substantial utility, and, in addition, lacks a "real-world" use. The Office additionally asserts the claimed invention lacks a "well-established utility."

It is respectfully submitted that the Office has erred in its analysis of substantial and credible utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. An assertion is credible unless the logic underlying the assertion is seriously flawed, or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. In this regard, the specification discloses at least one currently available use and the Office has acknowledged this use ("the specification contemplates that the transgenic mice can be used in a

method for identifying agents that modulate a biological response (e.g., thrombotic or pro-thrombotic)(page 25)", Office Action, page 4). Further, the transgenic mice and cells used to identify the agents are currently available. See, example 3. Since Applicants have specifically asserted the invention has a recited utility that is currently available for such use, the Office has erred in simply dismissing this assertion as wrong. The Office has failed to meet its burden of explaining either why the assertion is flawed, or why the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. If the Office maintains this rejection, the Office is respectfully requested to provide reasoning as to why the assertion of credible utility is flawed.

In addition, the Office has erred in dismissing Applicants' results in favor of the teachings of the prior art of record. The Office recites the teachings and demonstrated results disclosed in the specification and then dismisses the teachings and results over the art of record (Dong *et al.*, Blood 89: 4355-4363, 1997; and Kahn *et al.*, Blood 94: 4112-4121, 1999), asserting that the

> "claimed invention does not have a credible utility since one skilled in the art would not accept that the recited invention is currently available for use as claimed due to the uncertainty of the role that GP V plays in mammals due to the results displayed by the disclosure and Kahn showing that two transgenic mouse not expressing the GP V gene have different phenotypes."

Office Action, pages 4-5. Contrary to the position of the Office, the specification provides characterization of the role of GP V in mammals by disclosing the effect of GP V gene deletion in platelets and in transgenic mice. This characterization has been acknowledged by the Office ("the disclosure provides characterization of the effect of GP V gene deletion on thrombin-induced platelet function at low concentrations of thrombin (Example 5, pages 22-23), Office Action, page 4; and, "Furthermore in example 6, the specification displays the GP v-/- mice have a decrease bleeding time in vivo compared to +/+ mice (page 23-24)," Office Action, page 4). The Office also points to the teachings of Kahn, allegedly teaching two transgenic mice not expressing GP V have different phenotypes, compares the results to those obtained in the

specification and concludes Applicants' invention lacks credibility because Applicants' results differ from those of Kahn. However, it is well settled that the Office must accept Applicants' teachings and results unless there is reason for one skilled in the art to question the objective truth of the statements. Further, Kahn appears to have used different reagents and different methods of measurements/analyses. For example, Kahn did not appear to do statistical analysis of tail bleeding times as did Applicants (Kahn, figure 2 and Applicants, example 6). For measuring GPIb-IX surface expression, Kahn used GPIb-IX immune serum (provided by colleagues). Applicants used rabbit polyclonal antibody Ab# 3584. Therefore, Kahn's results may be attributable to the use of different reagents and methodologies.

The Office asserts the specification fails to disclose a substantial utility, a utility that defines a "real world use." The Office asserts that the art of record and the specification show that GP V deficiency in a transgenic mouse does not result or correlate to treating any disease with an agent, and cites BSS as an example. The Office further asserts that although the transgenic mouse of the claimed invention has a decreased bleeding time compared to a wild-type mouse, and a thrombin induced platelet function at low thrombin concentrations, a "real world" use is not established because there is no "real world" use for identifying agents that increase or decrease either characteristic.

The Office has erred in the analysis of substantial utility and real world use. The specification provides a substantial utility and real world use. The transgenic mice and platelets derived from the transgenic mice (-/-) have a decreased bleeding time *in vivo* as compared to the +/+ mice. The specification discloses assay methods using those mice, such as the tail-cut model, for determination of enhanced platelet function. The specification discloses that the increased aggregability of the platelets from the GP V -/- mice observed in the *in vitro* assays translates to a shorter bleeding time *in vivo* (page 24, lines 8-9). Contrary to arguments of the Office, there is a "real world" use for identifying agents which, for example, increase or decrease bleeding time. See, also, specification page 8, line 21 through page 9, line 4, disclosing use of cells, platelets,

tissues and whole organisms in testing the effects of various agents for their ability to reduce or increase GPIb-IX-V complex mediated processes such as arterial thrombosis. In addition, utility of the GP V transgenic mice is acknowledged by those of skill in the art. See, for example, the document by Kahn *et al.* (Kahn *et al.*, Blood 94(12): 4112-4121, 1999). Kahn states "The GPV-deficient mouse provides a critical reagent for probing the role of GPV in endothelial cells and for testing other hypothesis regarding GPV's function as they are generated." (Kahn, page 4119, last paragraph, last sentence).

Applicants have specifically asserted the invention has a particular utility and the Office has erroneously dismissed the assertions as being wrong. Applicants' asserted utility is credible and the invention is available for use. Reconsideration and withdrawal of all rejections stated above is respectfully requested.

Further Office arguments regarding written description are addressed, below.

Rejection under 35 U.S.C. § 112, first paragraph

At page 6 of the Office Action, the Office rejects claims 1-27 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is respectfully traversed. Claims 1, 3, 5, 10, 15, 21, 23 and 26 have been amended.

The Office understands claims 1-27 to be readable on a genus of non-human transgenic animals comprising either a modified, a non-functional or a disrupted glycoprotein GP V gene wherein the genus of the transgenic animal is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made. The Office understands claims 15-20 to be readable on a genus of a biological response of a non-human transgenic mammal modified GPV gene wherein the genus of the biological response is not

claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art. The Office understands claims 21-22 to be readable on a genus of a characteristic of an animal that is attributable to the expression of the GP V gene, wherein the genus of the characteristic is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the claimed invention was made. The Office asserts what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures that must exhibit the disclosed biological functions as contemplated by the claims. The Office asserts the claimed invention as a whole is not adequately described if the claims require essential or critical elements not conventional in the art as of Applicants' filing date.

Contrary to the arguments of the Office, the specification demonstrates possession by actual reduction to practice and by a description with sufficient relevant identifying characteristics to allow one of skill in the art to recognize Applicants were in possession of the claimed invention. The specification discloses the GP V nucleotide sequence from mouse (page 3, line 23, and Figure 1) and human (page 4, line 1). The specification discloses on page 21, lines 1-5, that mouse, rat and human sequences are known in the art. The specification discloses that the mouse and rat coding sequence are more homologous than human and mouse GP V sequences. The specification thus discloses the nucleotide sequences from a sufficient number of representative species were known in the art. The specification provides the mouse sequence. The specification further provides results showing the effect of knocking out GP V gene expression in a transgenic mouse. In light of the highly conserved nature of the gene, one of ordinary skill would find adequate guidance and written description to practice the invention across the full scope of the invention as claimed. Since the nucleotide sequences from a representative number of species were known or are presented and since the specification provides sufficient guidance enabling one of ordinary skill to make the transgenic mice, an adequate written description of the invention is provided thus demonstrating Applicants' possession of the full scope of the invention as claimed.

In view of the amendments to the claims and arguments above, it is believed the rejections have been overcome. Reconsideration and withdrawal of the rejections are respectfully requested.

At page 10 of the Office Action, the Office rejects claims 1-27 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office asserts the claimed invention is not supported by an asserted utility , specific, substantial or well established and lacks a written description and therefore one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended. However, Applicants disagree with the Office and Applicants' arguments addressing specific, substantial and credible utility stated above are incorporated herein.

The Office asserts the specification discloses only the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic mammals for use in the claimed invention. The Office asserts the state of the art at the time the application was filed for producing transgenic animals using pro-nuclear injection was unpredictable as exemplified by the prior art. The Office specifically cites to Polejaeva *et al.* (Polejaeva *et al.*, Theriogenology 53: 117-126, 2000) as discussing problems ("serious limitations") inherent in the production of transgenic animals by pronuclear injection and that, based on the teachings of Polejaeva, the production of the required phenotype coupled to germline transmission could require undue experimentation.

However, contrary to the position of the Office, the presence of "serious limitations" in a technique do not rise to the level of undue experimentation. The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended

period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " `The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. United States v. Telectronics Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). See, MPEP, August 2001, § 2164.06. In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis. Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. See, MPEP, August 2001, § 2164.06. The limitations discussed in the Office Action are routine problems encountered in experimental protocols and undue experimentation is not required for the production of transgenic animals having the desired phenotype.

The Office asserts the prior art and post-filing art indicate that ES technology is generally limited to the mouse system at present and that only "putative" ES cells exist for other species. The Office also asserts that the specification fails to teach the establishment of true ES cells for use in the production of any transgenic mammal other than mice and that one of skill cannot extrapolate from the specification and the prior art to any method of producing transgenic mammals comprising a modified GP V gene. The Office concludes undue experimentation would be required to reasonably extrapolate from random integration to determining if a DNA

sequence encoding the GP V polypeptide is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human mammal.

Applicants' arguments concerning undue experimentation are set forth above, and incorporated herein. The specification teaches production of a transgenic mouse by homologous recombination. Homologous recombination techniques are discussed at pages 9-10. Further, whether the DNA sequence is inserted at the correct site is easily determined by restriction analysis using Southern blotting (page 6, lines 7-13). Expression at a level sufficient enough to produce a phenotype is determined using any one of the methods disclosed in the specification: antibodies to the GP V protein, glycoprotein expression using flow cytometry, binding assays, platelet aggregation and bleeding time.

The Office has not established adequate reason why undue experimentation would be required in view of the disclosed methods and obtained results. If the Office maintains this rejection, the Office is respectfully requested to provide a detailed explanation of why undue experimentation would be required.

The Office asserts, at page 13, first full paragraph, the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of any transgenic mammal comprising a transgenic sequence encoding a modified GP V gene which expresses the transgenic sequence such that a phenotype occurs. The Office asserts the specification fails to describe any particular phenotype exhibited by any transgenic animal of the invention. The Office further asserts that one of skill would not be able to rely on the state of the art for an attempt to produce any transgenic mammal and that it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype.

Contrary to the position of the Office, the specification provides sufficient guidance to one of ordinary skill to practice the invention as claimed. Page 6 discusses methods for preparation of a

transgenic nonhuman animal using homologous recombination and thereafter, conventional breeding techniques to generate homo- and hetero-zygotes. Transgenic animals also encompass animals in which one or more cells are altered by or receive a recombinant, exogenous or cloned DNA molecule (page 7). The DNA molecule may be specifically targeted to a defined genetic locus, be randomly integrated within a chromosome, or it may be extrachromosomally replicating DNA (page 7). To prepare cells for recombination in the generation of transgenic animals, embryonic stem cells or a stem cell line may be obtained (page 10). The specification discloses cells other than embryonic stem cells can be utilized such as hematopoietic stem cells and cites to an issued US patent (5,589,369 to Seidman *et al.*) for further examples (page 10). The specification also discloses (page 10) that homologous recombination can proceed extrachromosomally and that such methods are described in issued US patent 5,721,367 (Kay *et al.*). At page 11, other methods for production of transgenic animals such as transfection, electroporation, microinjection, recombinant viral and retroviral infection are disclosed. Detailed procedures for producing trangenic animals are readily available to one skilled in the art (see, USPN 5,489,743 and USPN 5,602,307) (page 12). The specification (page 12) also discloses that although mice and rats may be the animal of choice for most transgenic experimentation, alternative animal species may be successfully used. The specification discloses that transgenic procedures have been successfully used in a variety of non-murine animals including sheep, goats, pigs, dogs, cats, monkeys, chimpanzees, hamsters, rabbits, cows and guinea pigs.

In view of the multitude of methods for production of transgenic animals disclosed in the specification, and the multitude of transgenic animals so produced in the art, the specification clearly provides guidance to one of skill in the art to practice the full scope of the invention as claimed. Reconsideration and withdrawal of the rejection is respectfully requested.

Further to the assertions by the Office (pages 13 and 14), methods for determining phenotypic expression are disclosed in the specification. Applicants' remarks concerning phenotypic

expression above, are incorporated herein by reference. The Office argues the specification fails to describe any particular phenotype exhibited by any transgenic animal of the invention. However, a phenotype for the claimed transgenic mice is disclosed on page 21. Platelets from transgenic mice did not have detectable GP V protein on the intact surface using FACS analysis or in total platelet lysates as determined by Western blotting. Thus, contrary to the arguments of the Office, the specification discloses a phenotype for the claimed transgenic mice. In addition, Applicants do not claim a particular level of expression (contrary to the Office assertions on page 16, lines 1-3). While expression is clearly controlled by a number of factors such as the promoter used, interactions with cis-and trans- acting elements and other factors, expression of the GP V protein would not require undue experimentation, lacking evidence to the contrary. One of ordinary skill would find adequate guidance and written description in the specification to practice the invention across the full scope of the invention. The Office has not met the burden of explaining why the invention is not enabled across the full scope of the invention.

At page 16 of the Office Action, the Office again points to the teachings of Kahn *et al.* stating that Kahn produces GP V deficient mice using gene targeting wherein the entire GP V gene was knocked out and shows that the mice responded normally to thrombin and that the tail bleeding times of wild-type and GP V deficient mice were indistinguishable. The Office argues that this is further support that the claimed invention is not enabled and that undue experimentation would be required to extrapolate to any transgenic mouse comprising a non-functional GP V gene, given that there is no evidence showing that the transgenic mouse in the claimed invention is a general phenomena. However, the Office has erred in not accepting Applicants' assertions of the obtained results. To the extent that Kahn's results differed from the results presented herein, those differences may be attributable to different methodologies and reagents used. See Applicants' discussion regarding Kahn, above.

At page 16 of the Office Action, the Office argues that claims 15-22 read on an *in vivo* method for identifying an agent that modulates a biological response of a non human animal comprising

a non-functional GP V gene, and that the specification and the state of the art do not provide sufficient guidance for one skilled in the art to monitor any biological response of an agent in an *in vivo* or *in vitro* assay. The Office further asserts that the specification and art do not provide sufficient guidance for one skilled in the art to reasonably correlate to any *in vitro* assays or *in vivo* assays without an undue amount of experimentation. However, contrary to the arguments of the Office, the specification discloses several assays used to detect GP V expression and those assays can be used irrespective of animal type. See examples 4-6. Applicants' arguments regarding undue experimentation set forth above, are incorporated herein. No undue experimentation is required.

The Office further asserts (page 17) that undue experimentation would be required to reasonably extrapolate to any characteristic of said transgenic mammal since no characteristics are enabled by the claimed invention. Applicants strongly disagree with the statement that no characteristics are enabled by the specification. The specification discloses results, showing characteristics of the GP V -/- transgenic mice, on pages 21-24. If the Office maintains this rejection, the Office is respectfully requested to explain why the phenotype of the GP V -/- mice is not considered a "characteristic."

The Office asserts, bottom paragraph at page 17, claims 15-22 are not enabling for a method of identifying an agent that modulates a biological response of a non-human transgenic animal. The Office further asserts it is not apparent from the specification what steps are required for determining whether an agent modulates the response. The Office concludes that an undue amount of experimentation would be required to reasonably extrapolate from the disclosure to make and/or use any method requiring the step of determining whether an agent modulates the response or a method of determining the effect of an agent on a characteristic of an animal that is attributable to the expression of the GP V gene.
Contrary to the arguments of the Office, undue experimentation is not required. Applicants' arguments above regarding undue experimentation are incorporated herein. The instant

specification provides the requisite amount of necessary guidance. The specification discloses (page 8) that the transgenic animals can be used to identify agents that modulate (either promote or further inhibit) GPIb-IX-V complex mediated processes. Page 8 discloses a variety of agents that can be tested, including several oral anticoagulants. Thus the specification envisions at least one method (oral administration) of administration as a step in a method of determining whether the agent modulates the response. The specification also states that evaluation of such agents can be conducted either *in vivo*, *in vitro* or *in situ* and that such techniques are known in the art. One of ordinary skill would find adequate guidance and written description to practice the invention across the full scope of the invention. The Office has not met the burden of explaining why the invention is not enabled across the full scope of the invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

At page 18 of the Office Action, the Office rejects claims 3, 5 and 15-22 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is respectfully traversed.

The Office argues claim 3 lacks antecedent bases for the limitation "the blood plasma of the animal." However, without acquiescing, claim 3 has been amended to remove the word "the." The amendment to claim 3 is believed to overcome the rejection and reconsideration and withdrawal is respectfully requested.

The Office argues that claims 5 and 16 are indefinite for recitation of the word "regenerating." However, without acquiescing, claims 5 and 6 have been amended to replace the word "regenerating" with the word "generating." The amendments to claims 5 and 16 are believed to overcome the rejection and reconsideration and withdrawal is respectfully requested.

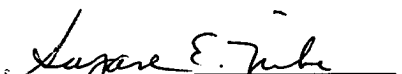
The Office argues that the word "determining" in claims 15-22 is a relative term which renders the claim indefinite. Contrary to the arguments of the Office, determining whether an agent modulates a biological response (claim 15) or determining the effect of an agent on a characteristic of an animal attributable to expression of a modified GP V gene (claim 22) is clearly within the skill in the art. See specification page 8, lines 16-20.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Reconsideration and the timely allowance of the pending claims is respectfully requested. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and § 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a Constructive Petition for Extension of Time in accordance with 37 C.F.R § 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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MARKED UP VERSION OF THE CHANGES TO THE SPECIFICATION

Claim 1 has been amended as follows:

1 (Once Amended). A nonhuman transgenic animal comprising a modified glycoprotein V (GP V) [GP V] gene, wherein said gene has been modified so that the animal does not express a functional GP V protein or expresses a GP V protein which demonstrates a reduced functionality as compared with the native or wild-type GP V protein.

Claim 3 has been amended as follows:

3 (Once Amended). Platelets isolated from [the] blood plasma of the animal of any of claims 1 or 2.

Claim 5 has been amended as follows:

5 (Once Amended). A method of preparing a nonhuman, transgenic mammal [with] comprising a modified glycoprotein V [GP V] gene, wherein said gene has been modified so that the mammal does not express a functional GP V protein or expresses a GP V protein which demonstrates a reduced functionality as compared with the native or wild-type GP V protein, said method comprising:

a) introducing into embryonic stem cells a nucleic acid molecule encoding a modified GP V gene; and

b) [regenerating] generating a transgenic nonhuman mammal from the cells [resulting from] of step a).

Claim 10 has been amended as follows:

10 (Once Amended). A method of preparing a nonhuman, transgenic mammal [with] comprising a nonfunctional glycoprotein V [GP V] gene, wherein said gene has been modified so that the mammal does not express a functional GP V protein or expresses a GP V protein which demonstrates a reduced functionality as compared with the native or wild-type GP V protein, said method comprising:

a) introducing into embryonic stem cells a nucleic acid molecule encoding a disrupted or nonfunctional GP V gene and a selectable marker;

b) identifying and selecting transformed cells;
c) injecting the transformed cells from step [c)] b) into blastocysts; and,
d) [regenerating] generating a nonhuman transgenic mammal from the blastocysts of step c), wherein the [regenerated] generated nonhuman transgenic mammal is chimeric for the disrupted or nonfunctional GP V gene.

Claim 15 has been amended as follows:

15 (Once Amended). A method to identify an agent that modulates a biological response of a nonhuman transgenic mammal having a modified glycoprotein V [GP V] gene, wherein said gene has been modified so that the mammal does not express a functional GP V protein or expresses a GP V protein which demonstrates a reduced functionality as compared with the native or wild-type GP V protein, comprising the step of exposing the mammal to the agent and determining whether the agent modulates the response.

Claim 21 has been amended as follows:

21 (Once Amended). A method of determining the effect of an agent on a characteristic of an animal that is attributable to the expression of the modified glycoprotein V [GP V] gene, wherein said gene has been modified so that the animal does not express a functional GP V protein or expresses a GP V protein which demonstrates a reduced functionality as compared with the native or wild-type GP V protein, said method comprising:

a) administering said agent to the animal of claim 1;
b) maintaining said animal for a desired period of time after said administration; and,
c) determining whether a characteristic of said animal that is attributable to the expression of the modified GP V gene has been affected by the administration of said agent.

Claim 23 has been amended as follows:

23 (Once Amended). [An] A cell line isolated from a nonhuman transgenic mammal that [contains] comprises a transgene stably integrated into the mammal's genome, said transgene encoding a modified glycoprotein V [GP V] gene, wherein said gene has been modified so that

the mammal does not express a functional GP V protein or expresses a GP V protein which demonstrates a reduced functionality as compared with the native or wild-type GP V protein.

Claim 26 has been amended as follows:

26 (Once Amended). The cell line of claim 25, wherein said mouse is fertile and transmits the [nonfunctional] modified GP V gene to its offspring.